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# COMPARISON OF ATOMIC FORCE MICROSCOPY & INVERSE GAS CHROMATOGRAPHY FOR THE PREDICTION OF DRY POWDER INHALATION PERFORMANCE

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## Introduction

- The relationship between particle-particle interactions & dry powder inhaler (DPI) fine particle fraction (FPF) has been the subject of much recent research.
- One approach that has proved successful is the measurement of cohesive-adhesive balance (CAB) ratios between drugs & excipients using atomic force microscopy (AFM) (1-3).
- A CAB ratio describes the cohesion between the particles of one material relative to its adhesion to another material. Such ratios have demonstrated a consistent relationship with DPI FPF (3).
- Another technique that has been widely studied is inverse gas chromatography (IGC). In the majority of this work, dispersive surface energy was measured, with mixed results.
- Tong *et al.* employed another IGC approach, by measuring Hansen solubility parameters, from which the strength of the adhesive & cohesive interactions within in a formulation could be calculated (4).
- Subsequently, these data were found to relate to the *in vitro* performance of DPI formulations (4).
- The aim of this study was to compare the data produced by these two techniques, which, in theory, should follow the same trends.

## Methods

- The AFM CAB ratios between five drugs & three carrier excipients (erythritol, lactose & mannitol) were measured using the usual method (2).
- The Hansen partial solubility parameters of these materials were determined by IGC (4) & the various cohesive & adhesive interactions between them calculated (5).
- This enabled IGC CAB ratios to be calculated, by dividing the drug-drug cohesive interaction by each drug-carrier adhesive interaction.
- Finally, the 15 possible carrier-based DPI formulations were produced using the study materials (1:67.5 drug:carrier) & their *in vitro* FPF quantified by aerosolisation from a Cyclohaler into a twin stage impinger at 60 l.min<sup>-1</sup>.

## Results

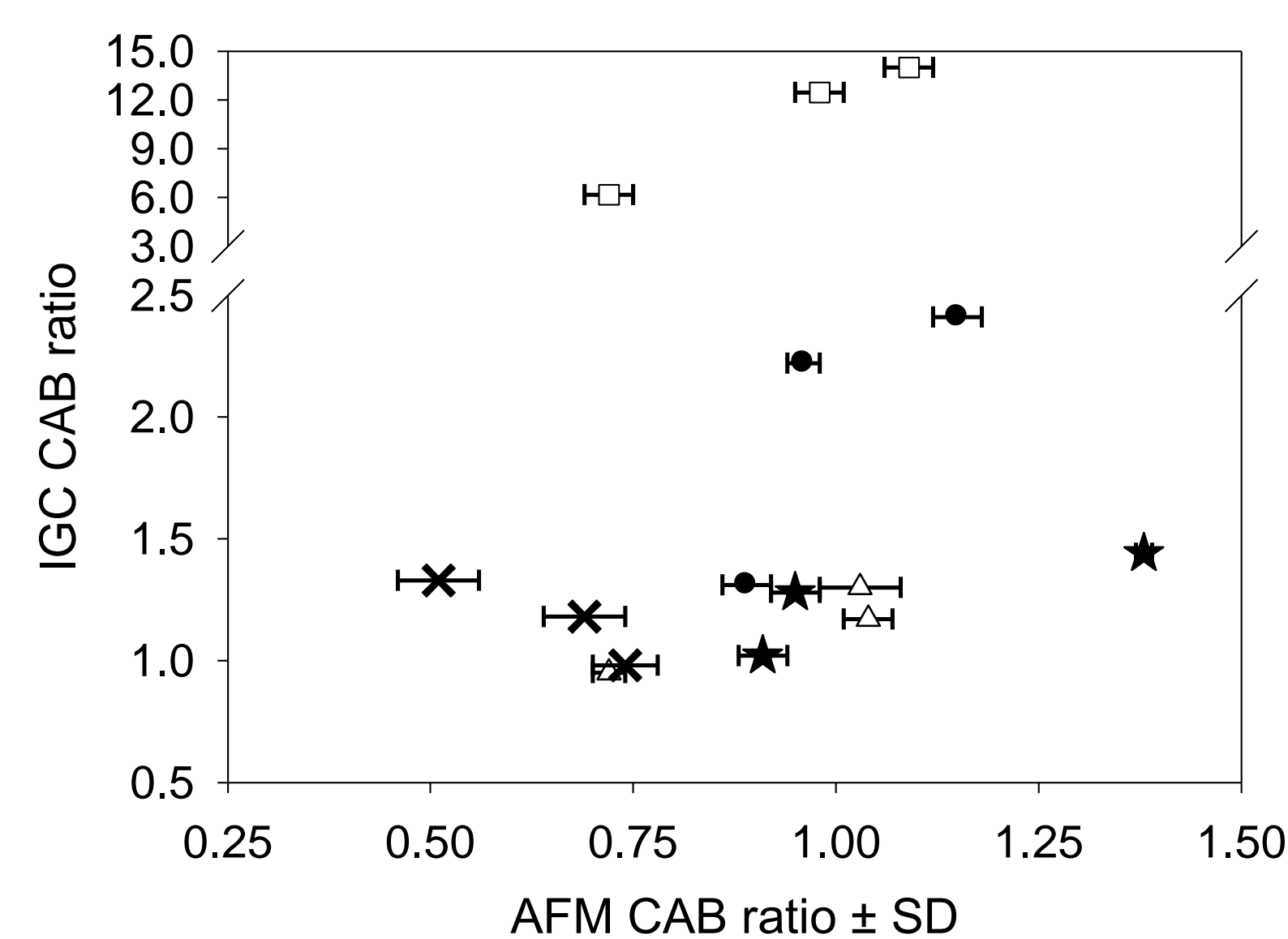


Figure 1: Comparison of IGC & AFM CAB ratios.

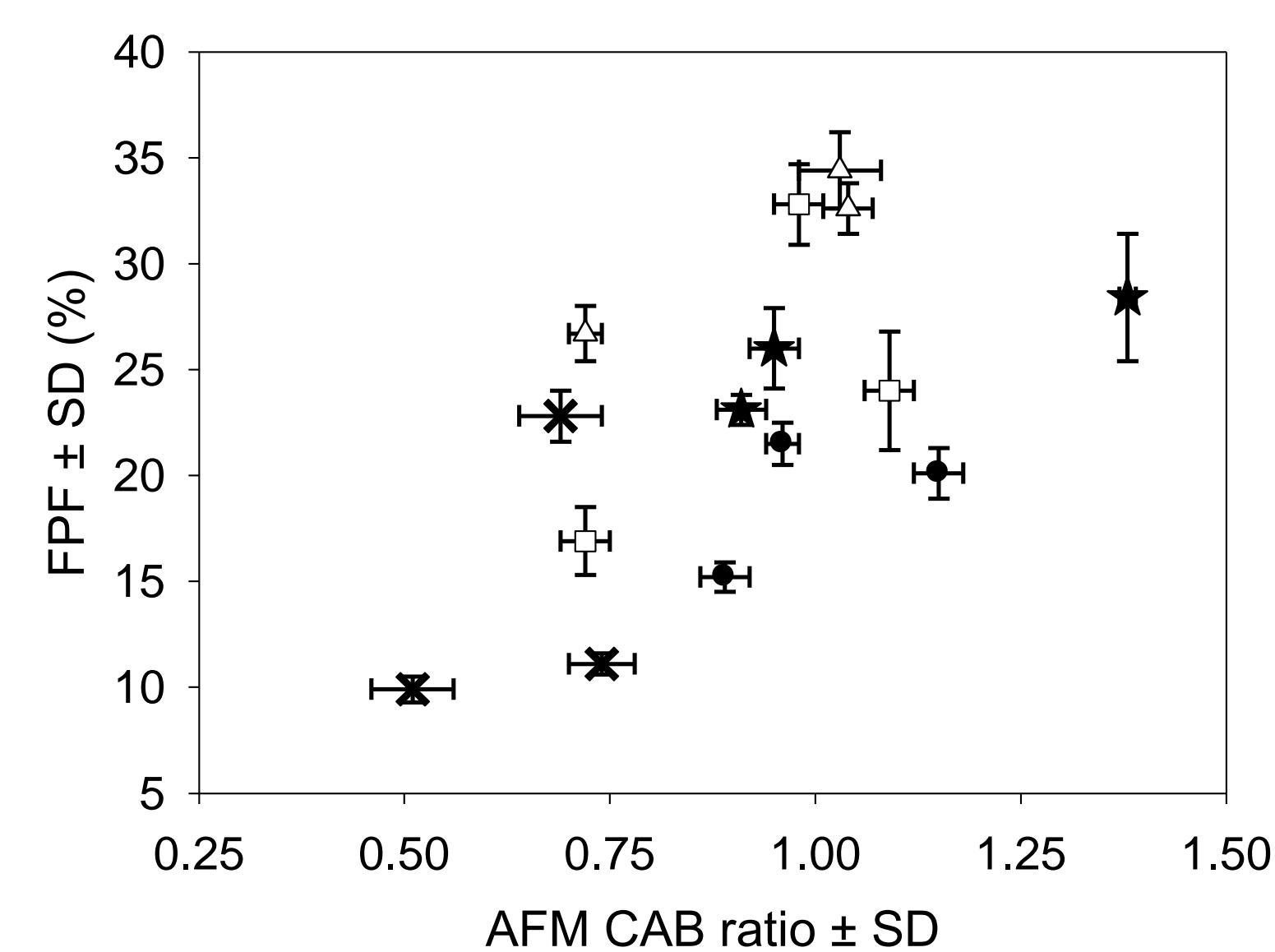


Figure 2: The relationship between FPF & AFM CAB ratio.

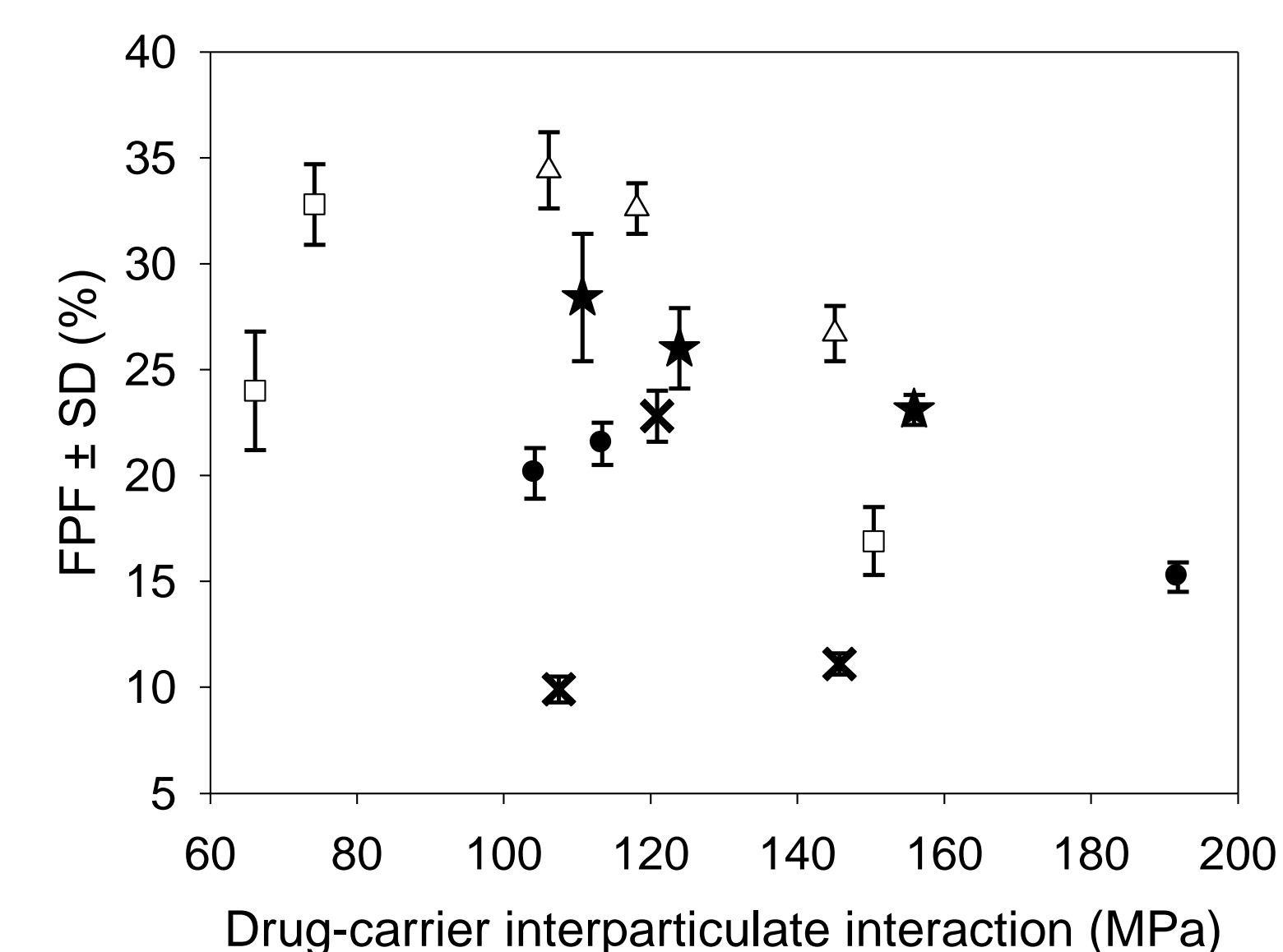


Figure 3: The relationship between FPF & drug-carrier interparticulate interaction strength as calculated from Hansen solubility parameters.

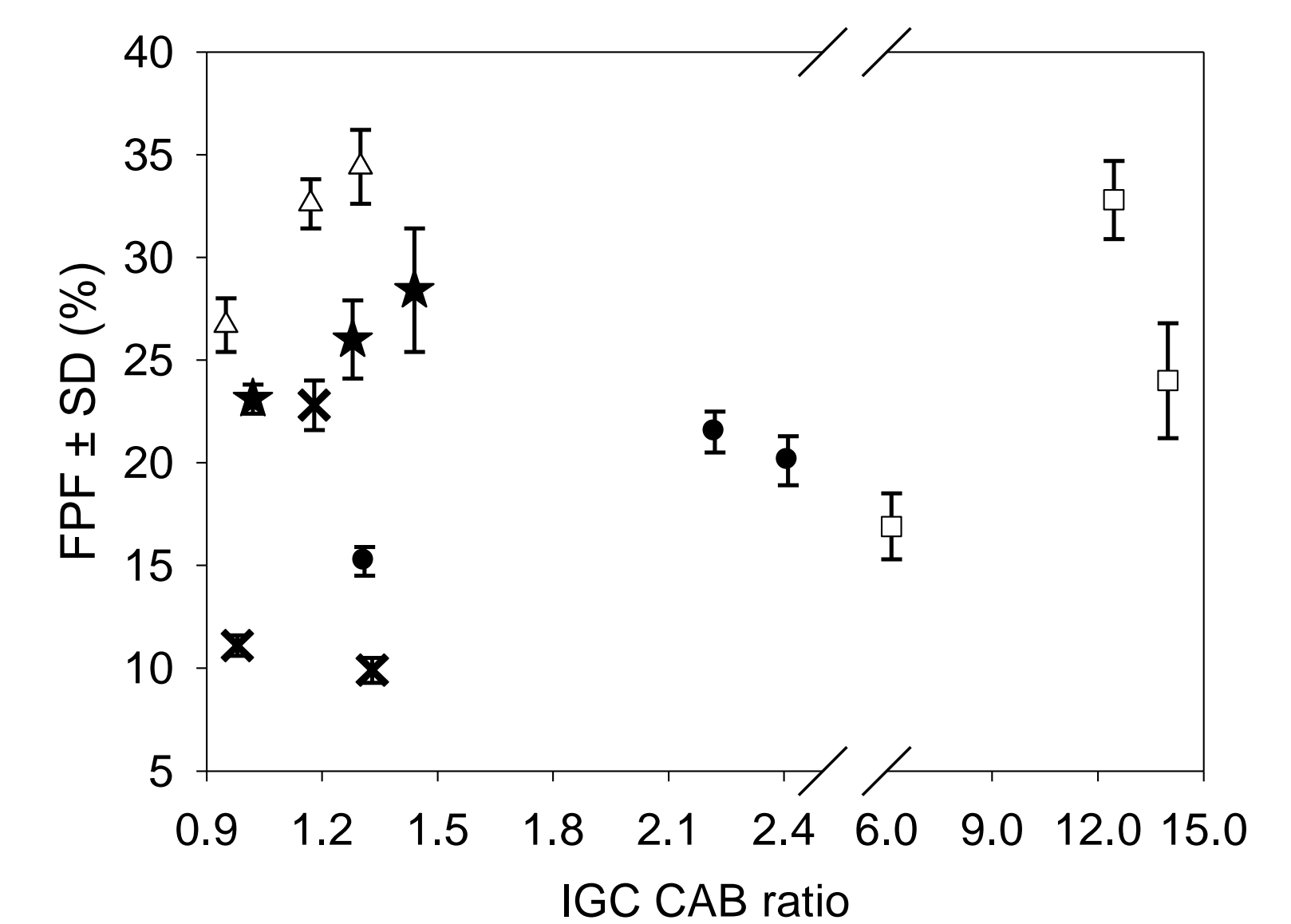


Figure 4: The relationship between FPF & IGC CAB ratios.

× - beclometasone dipropionate (BDP); ★ - budesonide; △ - salbutamol sulphate; □ - terbutaline sulphate; ● - triamcinolone acetonide

## Discussion

- The IGC CAB ratios were consistently larger than the AFM data (i.e. more cohesive). Figure 1 demonstrates that considering all the data, there was no correlation between the two sets of CAB ratios.
- If the data for each drug are considered separately, there is evidence for some correlation, with R<sup>2</sup> values ranging from 0.66 to 0.99. These represent a positive relationship for four of the drugs, but for BDP there was a negative relationship between the two sets of CAB ratios, i.e. as the AFM CAB ratio increased, the IGC CAB ratio decreased. There was no apparent explanation for this.
- Overall, this suggests that only for certain drugs the IGC technique employed is able to produce CAB ratios that follow the same pattern as those produced by the established AFM technique.
- When the data for four of the individual drugs in Figure 2 are considered, the previously observed relationship between FPF & AFM CAB ratio is observed, with slightly cohesive AFM CAB ratios being associated with the best fine particle delivery (3). The inconsistent BDP data may have resulted from the use of an inappropriate BDP crystal face for the AFM cohesion measurements (6).
- The relationship between FPF & drug-carrier interparticulate interaction (Figure 3) for four of the drugs also suggests an optimum point, as might be expected given the well characterised optimum in the FPF-AFM CAB ratio relationship (Figure 2).
- Given the inconsistent relationship between the AFM & IGC CAB ratios (Figure 1), it is unsurprising that Figure 4 does not reveal a consistent relationship between FPF & IGC CAB ratio.
- These results suggest that whilst there may have been a weak relationship between the AFM & IGC data, this was not strong enough to suggest that the two techniques were measuring exactly the same phenomenon or that they could be used interchangeably.

## References

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